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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Robin Torres

(Type or print name of person mailing paper)

Date: November 7, 1996

Robin Torres
(Signature of person mailing paper)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

NOV 25 1996

In re PATENT APPLICATION of)	Group Art Unit: 1211
)	
Chris Buhr et al)	Docket No. 157
)	
Serial No: 07/652,978)	Examiner: G. Kunz
)	
Filed: February 8, 1991)	
)	
Title: METHYLENE PHOSPHONATE)	
OLIGONUCLEOTIDE ANALOGS AND)	
NUCLEOSIDES)	

DECLARATION

The Assistant Commissioner
for Patents
Washington, D.C. 20231

Dear Sir:

I, Norbert Bischofberger, declare as follows:

1. I have been engaged in or directed the synthesis and chemistry of oligonucleotides, nucleotides and nucleosides for over ten years. I attach a copy of my Curriculum Vitae.
2. I am a coinventor of the above-referenced application.

3. I have read and believe I understand the Office Action Mailed August 7, 1996, in particular the rejection under 35 U.S.C. § 112, first paragraph.

4. I believe, more likely than not, that when we filed the application, it would have been obvious to one of ordinary skill in the art that, for claimed species where R^2 was phenyl, alkyl (1-12C) or hydrogentriethylammonium ion, such species were salts or synthetic intermediates useful to prepare the active compounds where R^2 is hydrogen. The amended claims recite compounds that are useful as salts of the biologically active compounds or as synthetic intermediates for preparing them. We prepared the biologically active compounds using diester intermediates as described in the working examples. We gave a general description of the synthetic method in Buhr et al. (*Collect. Czech. Chem. Commun.* 58:102-104 1993, of record, "Buhr"). Workers had described similar methods to prepare phosphonate nucleotide analogs where the synthesis procedure generated a diester phosphonate moiety as an intermediate (see, e.g., Jones and Moffatt, *J. Am. Chem. Soc.* 90:5337-5338, 1968, of record). Thus, it would have been obvious to one of ordinary skill in the art when we filed the application, that one would have converted the diesters to their corresponding diacids or salts to obtain biologically active nucleotide analogs.

5. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 10-24-1996
Gilead Sciences, Inc.
353 Lakeside Drive
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Norbert Bischofberger
Norbert Bischofberger

NORBERT BISCHOFBERGER, Ph.D.

TITLE	Vice-President of Research Gilead Sciences, Foster City, CA
RESPONSIBILITIES	Research Management, Coordination of Preclinical Development for Novel Drug Candidates, Investigation and Coordination of External Animal Model Studies, Facilitation of Library Organization and Management.
EDUCATION	Ph.D., Organic Chemistry at the Eidgenossische 1983 Technische Hochschule (ETH), Zurich, Switzerland B.S., Chemistry, University of Innsbruck, Austria 1979
EXPERIENCE	
1995 to Present	Vice-President of Research Gilead Sciences, Foster City, CA
1993 to 1995	Vice-President of Organic Chemistry Gilead Sciences, Foster City, CA
1990 to 1993	Director of Organic Chemistry Gilead Sciences, Foster City, CA
1988 to 1990	Manager of DNA Synthesis Genentech, Inc., South San Francisco, CA
1986 to 1988	Scientist, Chemistry Group, Molecular Biology Department Genentech, Inc., South San Francisco, CA
1984 to 1986	Harvard University, Postdoctoral Fellow Chemistry Department, Professor Whitesides Laboratory
1983 to 1984	Postdoctoral Fellow, Institute of Organic Chemistry Syntex, Inc.

AFFILIATIONS

American Chemical Society
American Association for the Advancement of Science

PUBLICATIONS

"Zur vinylogen b-Spaltung von Epoxy-enonen: Photoisomerisierung des 3,4:5,6-Diepoxy-5,6-dihydro-b-ionons." **Bischofberger, N.**, de Weck, G., Frei, B., Wolf, H.-R. and Jeger, O. *Helv. Chim. Acta* **1981**, 64, 1766-1776.

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"Effects of 16-Heterosubstitution on the Regiochemistry of the D-Homo Rearrangement." **Bischofberger, N.** and Walker, K.A.M. *J. Org. Chem.* **1985**, *50*, 3604-3609 .

"Cleavage of Single Stranded Oligonucleotides by EcoRI Restriction Endonuclease." **Bischofberger, N.**, Ng, P.G., Webb, T.R. and Matteucci, M.D. *Nucleic Acids Res.* **1987**, *15*, 709-716.

"Synthesis of 4-C Substituted Pyrimidine Nucleosides." **Bischofberger, N.** *Tetrahedr. Lett.* **1987**, *28*, 2821-2824 .

"Synthesis of Analogs of 1,3-Dihydroxyacetone Phosphate and Glyceraldehyde 3-Phosphate for Use in Studies of Fructose-1,6-diphosphate Aldolase." **Bischofberger, N.**, Waldmann, H., Saito, T., Simon, E.S., Lees, W., Bednarski, M.D. and Whitesides, G.M. *J. Org. Chem.* **1988**, *53*, 3457-3465.

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"Methylene Phosphonate Nucleoside Analogs and Oligonucleotide Analogs Made Therefrom." Buhr, C., Matteucci, M., Bischofberger, N., Froehler, B., # EP 570514, A1 931124, 1993.

"Thiepane Compounds Inhibiting and Detecting HIV Protease." Bischofberger, N., Kim, C., Krawczyk, S., McGee, L., Postich, M., Yang, W. U.S. Patent # ??

"Method and Cyclic Carbonates for Nucleotide Analogues." Bischofberger, N., Kent, K.M., U.S. Patent #5,514,798, May 7, 1996.

PRESENTATIONS AND ABSTRACTS

"Sequence Specific Gene Targeting." **Bischofberger, N.** Presentation Given at the *AAPS Western Regional Meeting*, Reno, Nevada 1991.

"Oligonucleotide-Based Recognition of Nucleic Acids and Proteins." **Bischofberger, N.** Presentation Given at the *ACS Carbohydrate Division Meeting*, San Francisco, California 1992.

"Inhibition of Viral Polymerases by Acyclic Phosphonmethylether Nucleosides." **Bischofberger, N.** Presentation Given at the *76th Canadian Society for Chemistry Conference and Exhibition*, Sherbrooke, Québec, Canada 1993.

"Evaluation of PMEA Efficacy in Macaques Chronically Infected with Simian Immunodeficiency Virus (SIV)." Follis, K., Tsai, C.-C., Grant, R., Sabo, A., **Bischofberger, N.** Presentation Given at the *11th Annual Symposium on Nonhuman Primate Models for AIDS*, 1993, Abstract.

"Evaluation of Nucleotide Prodrugs as Inhibitors of Viral Replication." **Bischofberger, N.**, et al. Presentation Given at the *International Society for Antiviral Research Meeting*, Venice, Italy 1993; Abstract, *Antiviral Res.*, 20, Sup. I, 142.

"Characterization of SIV Isolates from Macaques Treated with the Nucleoside Analog, 9-(2-Phosphonylmethoxyethyl)adenine (PMEA)." Sabo, A., Grant, R., Follis, K., **Bischofberger, N.**, Tsai, C.-C. Presentation Given at the *11th Annual Symposium on Nonhuman Primate Models for AIDS, 1993*, Abstract.

PRESENTATIONS AND ABSTRACTS (Continued)

"Comparison of the Efficacy of AZT and PMEA Treatment Against Acute SIVmne Infection in Macaques." Tsai, C.-C., Follis, K., Grant, R., Sabo, A., Nolte, R., Bartz, C., **Bischofberger, N.**, Benveniste, R. Presentation Given at the *11th Annual Symposium on Nonhuman Primate Models for AIDS, 1993*, Abstract.

"Comparison of Anti-HSV Activity and Metabolism of Acyclic Nucleotide Analogs." Aduma, P., Connelly, M., **Bischofberger, N.**, Fridland, A. Presentation Given at the *Seventh International Conference on Antiviral Research*, Charleston, South Carolina **1994** Abstract; *Antiviral Research*, Sup I, **23**, 41.

"Development of Nucleotide Prodrugs as Antiviral Agents", **Bischofberger, N.** Presentation Given at the *Seventh International Conference on Antiviral Research*, Charleston, South Carolina **1994**.

"Medicinal and Structural Chemistry Studies on GS522, a Potent Thrombin Inhibitor Discovered by Aptamer Selection", **Bischofberger, N.** Presentation Given at the *Eighth International Symposium on Purine and Pyrimidine Metabolism in Man Conference*, Bloomington, Indiana, **1994**.

"Structure-Function Relationship of Oligonucleotides Binding to Thrombin." **Bischofberger, N.** Presentation Given at the *11th International Round Table on Nucleosides, Nucleotides and their Biloogical Applications*, Leuven, Belgium, **1994**.

"Antiviral Efficacy in Mice of Oral Bis(POM) PMEA, the Bis(pivaloyloxymethyl) Ester Prodrug of 9-(2-Phosphonylmethoxyethyl)adenine." Naesens, L., Neyts, J., Balzarini, J., **Bischofberger, N.**, De Clercq, E. Presentation Given at the *International Conference on Antiviral Research*, Santa Fe, NM, Abstract, *Antiviral Research* **1995**, **26**, A276.

"Pharmacokinetics in Mice of Bis(POM) PMEA, the Bis(pivaloyloxymethyl) Ester Prodrug of 9-(2-Phosphonylmethoxyethyl)adenine." Naesens, L., Neyts, J., Balzarini, **Bischofberger, N.**, De Clercq, E. Presentation Given at the *International Conference on Antiviral Research*, Santa Fe, NM, Abstract, *Antiviral Research* **1995**, **26**, A277.

"Synthesis and Antiviral Activity of Novel Phosphonomethylether Nucleosides." **Bischofberger, N.**, Kern, E.R., Chen, M.S., Barkhimer, D.B., Cherrington, J.M., Dougherty, J.P., Kim, C.U., Lew, W., Mendel, D.B., Moon, K., Mulato, A.S., Williams, M.A., Yang, W. Presentation Given at the *International Conference on Antiviral Research*, Santa Fe, NM, **1995**, Abstract, *Antiviral Research*, Sup I, **24**.

PRESENTATIONS AND ABSTRACTS (Continued)

"Anti-Respiratory Virus Activity of Acyclic Phosphonomethylether Nucleosides." **Bischofberger, N.**, Barnard, D., Huffman, J.H., Kim, C.U., Lew, W., Sidwell, R.W., Williams, M.A., Yang, W. Presentation Given at the *35th ICAAC Conference*, San Francisco, CA, 1995, 26, A312, Poster.

"Efficacy of PMPA Against Simian Immunodeficiency Virus (SIV) Infection in Macaques as Models for Anti-HIV Therapies." Tsai, C-C., Beck, T., Sabo, A., Follis, K., **Bischofberger, N.** Presentation Given at the *NCCDG Conference*, Bethesda, MD, 1995, Abstract.

"Inhibition of Chronic SIV Infection in Cynomolgus Macaques: Comparison of AZT, PMEA and PMPA Treatments." Tsai, C-C., Follis, K., Sabo, A., Grant, R., Beck, T., **Bischofberger, N.** Presentation Given at *The 13th Annual Symposium on Nonhuman Primate Models for AIDS*, Monterey, CA, 1995, Abstract.

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"Prophylactic and Therapeutic Effects of 9-(2-Phosphonylmethoxypropyl)Adenine (PMPA) in Newborn Macaques Infected Orally with SIVmac." Van Rompay, K., Marthas, M., Beradi, C., Otsyula, M., Greenier, J., **Bischofberger, N.**, Pedersen, N. Presentation given at the *13th Annual Symposium on Nonhuman Primate Models for AIDS*, Monterey, CA, 1995, Abstract.

"Evaluation of 9-(2-Phosphonylmethoxypropyl)Adenine Antiviral Therapy for Acute Feline Immunodeficiency Virus Infection." Myles, M.H., **Bischofberger, N.**, Hoover, E.A. Presentation given at the *3rd International Feline Retrovirus Research Symposium*, Fort Collins, CO, March 6-9, 1996, Abstract.

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"Optimal Treatment Regimen for Preventing Acute SIV Infection Using PMPA in Macaques." Tsai, C.-C., Follis, K.E., Emau, P., Beck, T.W., Black, R., Benveniste, R., **Bischofberger, N.** Presentation given at the *14th Annual Symposium on Non-Human Primate Models for AIDS*, Portland, OR, October 23-26, 1996, Abstract.